REMARKS

Claim amendments

Claims 10, 19, 25, 31 and 39 have been amended to recite a method wherein the monoclonal antibody has the binding affinity for HIF as the monoclonal antibody 26-10 or a hypothalamic inhibitory factor antibody binding fragment thereof. Support for the amendment can be found in the specification, for example, on page 11, lines 6-11.

Rejection of Claims 10, 19, 25, 31 and 39 under 35 U.S.C. §112, first paragraph

Claims 10, 19, 25, 31 and 39 are rejected under 35 U.S.C. §112, first paragraph "because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description" (Office Action, page 2). The Examiner states that "[i]t is unclear is a cell line which produces an antibody having the exact chemical identity of **26-20** is known and publicly available, or can be reproducibly isolated without undue experimentation" and that "[w]ithout a publicly available deposit of the above cell line, one of ordinary skill in the are could not be assured of the ability to practice the invention as claimed" (Office Action, page 2). The Examiner further states that "[e]xact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic sequence is an unpredictable event" (Office Action, page 2). It is the Examiner's opinion that "it would require undue experimentation to reproduce the claimed antibody species **26-10**" and that "[d]eposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph" (Office Action, page 3).

Applicants respectfully disagree. In the specification as filed, Applicants teach that in a particular embodiment the monoclonal antibody for use in the methods of the present invention is the mAb 26-10 as described in Mudgett-Hunter, M., *et al., J. Immunol., 129L*1165-1172 (1982). Therefore, Applicants have provided evidence that the claimed biological materials are known and readily available to the public and reproducible from the written description. Nevertheless, in order to more clearly define the invention, Claims 10, 19, 25, 31 and 39 have been amended to recite a method wherein the monoclonal antibody has the binding affinity for HIF as the monoclonal antibody 26-10 or a hypothalamic inhibitory factor antibody binding fragment thereof.

Applicants have provided an enabling disclosure for the full scope of the subject matter of the claimed invention, particularly as amended.

Rejection of Claims 1-5, 7-14, 16-20 and 33 under 35 U.S.C. §103(a)

Claims 1-5, 7-14, 16-20 and 33 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Haupert, Jr. in view of Montali et al. and Cordle et al., 4,897,465" (Office Action, page 6). The Examiner stated that it would have been obvious to one of ordinary skill in the art to substitute the initial chromatography method of Haupert, Jr. with the diafiltration method of Cordle, *et al.* because Cordle, *et al.* teach that diafiltration reduces the filterable components in a retentate and thus results in a highly purified concentrate. Further, the Examiner stated that it would have been obvious to one of ordinary skill in the art to substitute the affinity chromatography purification step of HIF in Haupert, Jr. with the immunoaffinity chromatography step in Montali, *et al.* because both Montali, *et al.* and Haupert, Jr. establish that affinity chromatography and immunoaffinity chromatography are essentially equivalent techniques for purifying and isolating HIF.

Applicants' claimed invention is directed to a method of purifying hypothalamic inhibitory factor (HIF) from a sample containing HIF. The method includes combination of diafiltration, solid phase extraction and immunoaffinity chromatography steps.

Haupert, Jr. teaches methods for isolating HIF by lipophilic gel chromatography followed by further purification using successive cation and anion exchange chromatographies. Thereafter, affinity chromatography is employed, followed by a reverse phase HPLC chromatography step.

As stated by the Examiner, Haupert, Jr. does not disclose using diafiltration or immunoaffinity chromatography as purification and isolation techniques. Further, Haupert, Jr. does not disclose or suggest diafiltration as an alternative to lipophilic gel chromatography to purify HIF. Haupert, Jr. also does not disclose or suggest combination of diafiltration with solid phase extraction and immunoaffinity chromatography to purify HIF.

Cordle *et al.* teach "an ultrafiltration process for enriching and concentrating a desired protein from a fluid containing various proteins" using "two successive ultrafiltrations" wherein the pH between the two successive ultrafiltrations are shifted "in order to remove materials of lower molecular weight or higher molecular weight than the desired protein on the basis of charge as well as size" (Cordle *et al.*. Column 4, lines 33-43). Cordle *et al.* teach that the

retentate of the ultrafiltration which contains the protein (*i.e.*, from the first or second ultrafiltration) "may be submitted to diafiltration . . ." (Cordle *et al.*, column 5, lines 17-45; in particular column 5, lines 18-19 refers to use of diafiltration when the retentate of the first ultrafiltration contains the protein, and column 5, lines 39-40 refers to the use of diafiltration when the retentate of the second ultrafiltration contains the protein). According to Cordle *et al.*, the "diafiltration of the fraction containing the desired protein can be performed to enrich the fraction . ." (Cordle *et al.*, column 4, lines 43-45).

Thus, Cordle *et al.* teach purification of ***large, high molecular weight protein*** molecules wherein diafiltration is used to produce a ***diafiltrate retentate*** comprising the protein. In contrast, Applicants teach purification of ***small molecular weight HIF molecules*** wherein diafiltration is used to "to produce a ***diafiltrate permeate*** comprising the HIF" (specification, page 3, lines 27-28). As Cordle *et al.* point out:

> the product which passes through the membrane is known as the ultrafiltrate or "permeate". The constituents which are held back or retained are known as the "retentate" (Cordle *et al.*, column 4, lines 65-68).

The Examiner states that it would have been obvious to one of ordinary skill in the art to substitute the initial chromatography method of Haupert, Jr. with the diafiltration method of Cordle, *et al.* because Cordle, *et al.* teach that diafiltration reduces the filterable components in a retentate and thus results in a highly purified concentrate. Applicants respectfully disagree. Based on the teachings of Cordle *et al.*, it would ***not*** have been obvious to one of ordinary skill in the art to substitute the initial chromatography method of Haupert, Jr. with the diafiltration method of Cordle *et al.* to purify small molecular weight HIF molecules, ***because HIF would not be present in the highly purified concentrate (i.e., the diafiltration retentate)***. As Applicants point out, ***HIF is present in the diafiltration permeate***. As the court has clearly stated, "[t]he mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification" (*In re Gordon*, 221 U.S.P.Q. 1125, 1127 (CAFC 1984). In the present case, the prior art does not suggest the desirability of substituting the initial chromatography method of Haupert, Jr. with the diafiltration method of Cordle *et al.* to purify small molecular weight HIF molecules because the HIF would not be present in the highly purified concentrate of the diafiltration.

There is no disclosure or suggestion in Cordle *et al.* of employing diafiltration to purify HIF. Further, as with Haupert, Jr., there is no disclosure or suggestion that diafiltration could be employed as a substitute for an initial chromatography step, such as a lipophilic gel chromatography step, to purify HIF. There is also no disclosure or suggestion that diafiltration could be combined with solid phase extraction and immunoaffinity chromatography steps to purify HIF, as claimed by Applicants.

As stated by the Examiner, Montali *et al.* teach a method for purifying endogenous digitalis-like factor, i.e., HIF. The method taught by Montali *et al.* includes use of an immunoaffinity chromatography system of high-affinity antibodies bound to sepharose.

Contrary to the Examiner's statement, there is no disclosure in either Montali *et al.* or Haupert, Jr. that affinity chromatography and immunoaffinity chromatography are essentially equivalent techniques for purifying and isolating HIF. Moreover, even if one of ordinary skill in the art would expect, at the time the instant application was filed, that immunoaffinity chromatography could be employed as an equivalent technique to the affinity chromatography described in Haupert, Jr., Montali *et al.* do not remedy the deficiencies of Haupert, Jr. and Cordle *et al.* that have been discussed above.

For example, there is no disclosure or suggestion in Montali *et al.* of diafiltration to separate HIF from a sample containing HIF, as claimed by Applicants. There is also no disclosure or suggestion that diafiltration can be employed as an alternative to lipophilic gel chromatography in a series of steps employed to purify HIF, and there is no disclosure or suggestion of combining diafiltration with immunoaffinity chromatography to purify HIF.

As discussed above, none of the references cited by the Examiner, taken either separately or in combination, discloses or suggests purifying HIF by combining the method steps of diafiltration, solid phase extraction and immunoaffinity chromatography, as claimed by Applicants. Therefore, Applicants' claimed method for purifying HIF meets the requirements of 35 U.S.C. § 103(a).

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

10. (Amended) The method of Claim 9 wherein the monoclonal antibody [is] has the binding affinity for HIF as the monoclonal antibody 26-10 or a hypothalamic inhibitory factor antibody binding fragment thereof.

19. (Amended) The method of Claim 18 wherein the monoclonal antibody [is] has the binding affinity for HIF as the monoclonal antibody 26-10 or a hypothalamic inhibitory factor antibody binding fragment thereof.

25. (Amended) The method of Claim 24 wherein the monoclonal antibody [is] has the binding affinity for HIF as the monoclonal antibody 26-10 or a hypothalamic inhibitory factor antibody binding fragment thereof.

31. (Amended) The method of Claim 28 wherein the monoclonal antibody [is] has the binding affinity for HIF as the monoclonal antibody 26-10 or a hypothalamic inhibitory factor antibody binding fragment thereof.

39. (Amended) The method of Claim 38 wherein the monoclonal antibody [is] has the binding affinity for HIF as the monoclonal antibody 26-10 or a hypothalamic inhibitory factor antibody binding fragment thereof.